REMARKS

I. In item 2 of the Office Action, claims 1-3, 8, 27, 28, 30, 31 and 43-47 were rejected under 35 U.S.C. §102(b) over WO 99/26480.

The rejection is traversed for the following reasons.

1. As provided in the record, case law holds that a genus does not necessarily enable and teach all species encompassed therein, particularly one species of a divergent genus where the particular species is not highlighted, Kollman, Kalm and Ruschig, of record.

WO 99/26480 teaches at page 5, a wide range of vectors. Then at pages 11-15, possibly all conceivable means for administering a biological drug are provided. An artisan would have a large list of vectors and delivery means from which to choose and to test to obtain the instantly claimed invention. There is no highlighting of and no enabling teaching of direct administration of an endostatin-expressing vector to the eye as claimed in the instant application.

Because ocular treatment by particular vectors is but one embodiment of many included in a generic listing and that embodiment is not highlighted and taught beyond mere mention in a generic listing, anticipation does not lie.

2. A reference also must be considered for all that is fairly suggested therein. In re Baird, 16 F.3d 380, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994).

As noted in the paragraph bridging pages 13 and 14 of WO 99/26480, transfer of the nucleic acid is the critical first step in gene therapy, "Since transfer of the nucleic acid to appropriate target cells represents the critical first step in gene therapy, choice of the particular gene delivery system will depend on such factors as the intended target and the route of administration, e.g., locally or systemically."

However, no particular teaching of how to deliver endostatin to the eye using a vector is provided in WO 99/26480. The working examples relate to angiostatin or an angiostatin fusion and to treating cancer. The reference thus suggests angiostatin for treating cancer.

Because WO 99/26480 does not teach how to use endostatin and the reference as a whole enables angiostatin instead, WO 99/26480 cannot anticipate the claimed invention relating to use of endostatin in the eye.

3. Applicants also note that a reference must be considered as a whole, it is improper to pick and to choose portions of a reference and to take those portions out of context.

SmithKline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878, 8 U.S.P.Q.2d 1468 (Fed. Cir. 1988); Bausch & Lomb, Inc. v. Barnes-Hind Hydrocurve, Inc., 796 F.2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987).

WO 99/26480 teaches without enablement, except for actual angiostatin expression in Example 4 and an angiostatin-endostatin fusion in Example 5, a vast range of embodiments. It is improper, and clearly with hindsight that the Examiner single out one embodiment of many, one embodiment that is not enabled or reduced to practice, and then assert that embodiment is placed in the hands of the public. Moreover, WO 99/26480, focusing on angiostatin, teaches away from endostatin, Bausch & Lomb, at 449.

Also, the teaching in the paragraph bridging pages 13 and 14 of WO 99/26480 discussed above speaks to one not taking a particular teaching out of a general disclosure, absent evidence, such as a working example, as proof of an enabling embodiment.

Therefore, for yet another reason, novelty of the instant invention is not destroyed by WO 99/26480.

4. To be effective, a reference must be enabling, the reference must place the claimed subject matter in the possession of the public. Paperless Accounting, Inc. v. Bay Area Rapid Transit Sys., 804 F.2d 659, 231 U.S.P.Q. 649 (Fed. Cir. 1986) cert denied, 480 U.S. 933 (1987); Rockwell International Corp. v. United States, 147 F.3d 1358, 47 U.S.P.Q.2d 1027 (Fed. Cir. 1998).

As argued herein and in the record, WO 99/26480 is not enabled for ocular gene therapy with endostatin.

WO 99/26480, as a whole, teaches, at best, expression of angiostatin with a goal of treating cancer. WO 99/26480 does not provide a specific teaching of how to obtain ocular gene therapy with endostatin.

Moreover, the references of record teach that factors that modulate angiogenesis are distinct; any one factor acts preferentially on a particular target organ, tissue or cell; any one factor can have different activities in different organs, tissues or cells; and the activity of any one factor can vary depending on the environment, metabolic state etc.

Because WO 99/26480 does not particularly teach making and using endostatin, does not particularly teach treating non-cancer disorders and does not particularly teach the eye as the

target organ, WO 99/26480 is not enabling as to ocular gene therapy with endostatin and thus does not anticipate the claimed invention.

5. WO 99/26480 is not an issued patent and, thus, there is no presumption of patentability. It follows, then, that there also is no presumption of enablement.

As mentioned above, the expressed recombinant proteins taught in the working examples of WO 99/26480 were angiostatin and an angiostatin/endostatin fusion molecule. All of the remainder of the working examples are prophetic, relating to treating cancer.

Those prophetic examples relating to treating cancer are not enabled and are inoperative. Attached hereto is a document regarding attempts to treat cancer with endostatin. The first named inventor of WO 99/26480, Phillipe Leboulch is quoted in the article, "We could not see an effect of endostatin any way we tried."

That is clear evidence the prophetic examples relating to treating cancer with endostatin are not enabled. Therefore, WO 99/26480 is not enabling on the use of endostatin and thus cannot anticipate the claimed invention.

WO 99/26480 is not an effective reference as to the instant invention. Clearly, WO 99/26480 does not provide an enabling teaching as to ocular gene therapy with endostatin. Thus, WO 99/26480 does not place the claimed invention enably in the hands of the artisan. Hence, there is no anticipation. Accordingly, withdrawal of the rejection is requested respectfully.

II. On pages 3-9 of the Office Action, claims 1 and 29; claims 1 and 32; claims 1, 33 and 38; and claims 1, 33, 38-41 and 48-50 were rejected under 35 U.S.C. §103(a) over four combinations of references. In each of the four rejections, WO 99/26480 is the primary reference. The Examiner detailed a number of deficiencies in WO 99/26480 in constructing the four rejections.

The four rejections are traversed for the following reasons.

As discussed in Section I hereinabove, and in the record, and herein incorporated by reference, WO 99/26480 is not enabled as to the claimed invention and thus is legally insufficient to teach or suggest ocular gene therapy using endostatin, Rockwell, supra, at 1365.

For that reason alone, because the primary reference is legally insufficient for all four rejections, prima facie cases of obviousness have not been made.

WO 99/26480 does not provide any direction or guidance to choose from amongst the range of options taught therein to provide the artisan with sufficient enabling guidance such that the artisan would have at the time of the invention a reasonable expectation of successfully obtaining the use of endostatin for ocular gene therapy. In re O'Farrell, 853 F.2d 894, 7 U.S.P.Q.2d 1973 (Fed. Cir. 1988).

None of the secondary or tertiary references cures the fatal deficiencies of WO 99/26480. Therefore, a prima facie case of obviousness was not made in any of the four rejections.

For example, Keshet et al. do not relate to ocular disorders. Keshet et al. relate to cancer. As provided in the record, angiogenesis is a very diverse process from tissue to tissue and from cell to cell. Thus, absent evidence of a correlation, there is no basis to conclude that the stimulation or inhibition of angiogenesis by a factor in one disorder, in one tissue or in one cell will be operable in another disorder, another tissue or another cell. Accordingly, Keshet et al. do not cure the deficiencies of the primary reference. Keshet et al. do not enable use of endostatin for ocular gene therapy.

Otani et al. do not relate to gene therapy and do not relate to cancer. Therefore, Otani et al. is from non-analogous art as to WO 99/26480 or Keshet et al. Otani et al. do not cure or enable WO 99/26480.

In all of the four rejections of alleged obviousness, the issue is whether an artisan would have a reasonable expectation of successfully obtaining ocular therapy for a non-cancerous condition using endostatin. The evidence of record and attached hereto demonstrate that an artisan would not have a reasonable expectation of success because the primary reference does not enable and thus does not teach use of endostatin in a vector to treat ocular neovascularization. Angiogenesis, and the inhibition thereof, in cancer and in non-cancer conditions is diverse, and the factors that stimulate and inhibit angiogenesis are diverse, see Rockwell, supra, at 1365.

Moreover, merely combining elements from the prior art without some teaching to do so is contrary to the statute, SmithKline, supra, at 887. WO 99/26480 teaches away from and does not enable endostatin for ocular use. The secondary references do not cure that deficiency.

Accordingly, prima facie cases of obviousness have not been made. There is no enablement and no reasonable expectation of success in the use of endostatin, in general, and in particular, in the eye, for treating a non-cancer condition. Hence, withdrawal of the four §103(a) rejections is requested respectfully.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance and early indication of such is requested respectfully. Reexamination, reconsideration, withdrawal of the rejections and early passage of the application to issuance are solicited earnestly. If any fees are found to be applicable, please charge any additional fees or make any credits to Deposit Account No. 02-1818.

Respectfully submitted,

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